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Atypical antipsychotics and hyperglycemic emergencies: Multicentre, retrospective cohort study of administrative data☆

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ABSTRACT

Objective: To evaluate the relationship between initiation of atypical antipsychotic agents and the risk of hyperglycemic emergencies.
Method: We conducted a multicentre retrospective cohort study using administrative health data from 7 Canadian provinces and the UK Clinical Practice Research Datalink. Hospitalizations for hyperglycemic emergencies (hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic state) were compared between new users of risperidone (reference), and new users of olanzapine, other atypical antipsychotics, and typical antipsychotics. We used propensity scores with inverse probability of treatment weighting and proportional hazard models to estimate the site-specific hazard ratios of hyperglycemic emergencies in the year following drug initiation separately for adults under and over age 66 years. Site-level results were pooled using meta-analytic methods.
Results: Among 725,489 patients, 55% were aged 66+ years; 5% of younger and 19% of older patients had pre-existing diabetes. Rates of hyperglycemic emergencies were low (0.1–0.2%) and similar between sites. The risk of an event was significantly lower with other atypical (99% quetiapine) compared to risperidone use in older patients [adjusted hazard ratio, 95% confidence interval (CI): 0.69, 0.53–0.90].
Conclusions: Risk for hyperglycemic emergencies is low after initiation of antipsychotics, but patients with pre-existing diabetes may be at greater risk. The risk appeared lower with the use of quetiapine in older patients, but the clinical significance of the findings requires further study.

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1. Introduction

Atypical antipsychotic agents are first-line therapy for symptoms of schizophrenia and other psychotic disorders. However, numerous studies have documented a higher incidence of diabetes and hyperglycemia among patients treated with atypical antipsychotics (at least partially attributed to effects of weight gain) compared to typical agents (Caro et al., 2002; Koller and Doraiswamy, 2002; Kornegay et al., 2002; Koro et al., 2002; Sernyak et al., 2002; Buse et al., 2003; Gianfrancesco et al., 2003a, 2003b; Lindenmayer et al., 2003; Citrome et al., 2004; Leslie and Rosenheck, 2004; Gianfrancesco et al., 2006; Ramaswamy et al., 2006; DuMouchel et al., 2008; Smith et al., 2008). In addition, case reports and case series have suggested that these drugs may also have acute hyperglycemic effects, occasionally leading to diabetic ketoacidosis (DKA), coma, and death (Muench and Carey, 2001; Roefaro and Mukherjee, 2001; Jin et al., 2002; Koller et al., 2003; Wilson et al., 2003; Koller et al., 2004; Takahashi et al., 2005; Marlowe et al., 2007; Kohen et al., 2008; Makhzoumi et al., 2008). However, these infrequent, but serious adverse effects have been difficult to quantify.

In a recent population-based study of Ontario seniors, new exposure to antipsychotic therapy was associated with an increased risk of hospitalization for hyperglycemia or diabetes among patients with (Lipscombe et al., 2009) and without pre-existing diabetes (Lipscombe et al., 2011). In those with diabetes, the strength of the association declined with increasing duration of use (Lipscombe et al., 2009). While these findings are suggestive of acute metabolic effects, the studies had insufficient power to isolate the risk of life-threatening hyperglycemic emergencies, such as DKA, from that of diabetes. In addition, controversy exists regarding whether the risk of hyperglycemia varies depending on the type of antipsychotic agent. There is some evidence that olanzapine may be associated with a higher risk than risperidone (Ramaswamy et al., 2007), but data are limited.

The Canadian Network for Observational Drug Effect Studies (CNODES) (Suissa et al., 2012), a newly-formed collaboration of eight independent research teams with access to administrative data provides a unique opportunity to study these rare but important effects. Accordingly, we used the healthcare records of over 725,000 patients to quantify the association between new treatment with different antipsychotic agents and hospitalization for an acute hyperglycemic emergency.

2. Method

2.1. Setting and source population

We used a common analytical protocol to conduct the study in seven Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, and Nova Scotia), with a total source population of approximately 34 million, and the United Kingdom General Practice Research Database (GPRD, since renamed Clinical Practice Research Datalink or CPRD), which contains health records for approximately 12 million residents. The study population consisted of patients aged 18 years or older who were newly treated with an antipsychotic medication between April 1, 1997 and March 31, 2010. In three provinces (Nova Scotia, Ontario, and Alberta), drug exposure data were available only for patients aged 65 years and older.

2.2. Data sources

All Canadian centres contributed information from their respective provincial administrative health care databases. Prescription drug claims included patient-level records specifying, at minimum, the name and quantity of each medication and the date that the medication was dispensed. Physician service claims and hospitalization records included the date of each service encounter or admission, 1 to 25 International Classification of Disease (ICD)-9 or ICD-10 diagnosis codes, and physician service or hospital procedure codes, as appropriate. The GPRD captures drug prescriptions (rather than dispensations), and several data elements not available in the Canadian databases, including laboratory test results, body mass index, and smoking status. All of the databases have been used extensively in observational research.

2.3. Cohort creation

In each jurisdiction, patients from the source population were included in the cohort if they were newly dispensed an antipsychotic medication between April 1, 1998 (or one year after the beginning of data availability) and March 31, 2010. New exposure was defined as no prescription for an antipsychotic in the preceding 365 days. The date of the first new exposure during the study period was defined as the cohort entry date.

Patients were excluded if, on the cohort entry date, they were less than 18 years of age (or 66 years of age in the provinces where drug benefit coverage started at age 65), had fewer than 365 days of enrollment in their health plan, resided in a nursing home, or received more than one antipsychotic medication. Patients also were excluded if they were hospitalized with the primary study outcome within 30 days preceding cohort entry, were hospitalized for greater than 30 consecutive days in the year preceding cohort entry, or received renal dialysis or palliative care in the year preceding cohort entry.

2.4. Exposure definition

Drug exposure was determined at cohort entry based upon the first antipsychotic medication received — i.e., all analyses were based on an intention-to-treat principle. The reference exposure was risperidone, as it was the most frequently used antipsychotic and is thought to be associated with a lower risk of hyperglycemia (Ramaswamy et al., 2007). The other exposure groups were: olanzapine, the remaining atypical antipsychotics collectively, and all remaining 'typical' antipsychotics (e.g., haloperidol, phenothiazines). The specific agents, routes, and corresponding Anatomical Therapeutic Chemical (ATC) classifications are listed in Appendix 1.

2.5. Definition of the primary outcome measure: hyperglycemic emergency

We defined a hyperglycemic emergency as the first hospital admission in the 365 days following drug initiation (cohort entry) that was associated with a pre-admission diagnosis of hyperglycemia, DKA, or hyperglycemic hyperosmolar state (HHS) using the ICD-9 and ICD-10 diagnosis codes listed in Appendix 2. In all analyses the date of hospital admission served as the outcome event date.

2.6. Statistical analysis

Our analyses comprised one primary and two secondary pair-wise comparisons of the risk of a hyperglycemic emergency, with risperidone serving as the reference group throughout. Due to evidence of greater weight gain and diabetes risk with olanzapine (Allison and Casey, 2001; Ramaswamy et al., 2007), the primary comparator was olanzapine. The secondary comparisons were with other atypical antipsychotics and typical antipsychotics, respectively.

In each comparison, we employed inverse probability of treatment weighting (IPTW) using a propensity score to estimate marginal treatment effects (Austin, 2011). The propensity score represented the predicted probability of treatment with the comparator antipsychotic (versus risperidone) based upon a set of baseline patient characteristics that we believed could influence the risk of a hyperglycemic emergency. Propensity scores were estimated using logistic regression models in which treatment with the comparator antipsychotic was regressed on age, sex, and the following pre-specified covariates: calendar year of cohort entry; history of diabetes, schizophrenia, and dementia;

neighbourhood income quintile; Romano Comorbidity Index (Schneeweiss et al., 2001); number of hospitalizations, outpatient family physician consultations and outpatient psychiatric consultations in the year preceding cohort entry; and concurrent exposure to selected drugs that are markers of disease or could influence glucose control. The CPRD team added smoking status, alcohol consumption, and body mass index.

We estimated the absolute difference in the probability of a hyperglycemic emergency within 365 days of drug initiation. To estimate the effect of the comparator antipsychotic agent versus risperidone, the cause-specific hazard for the comparator was estimated by using a Cox proportional hazards regression model to regress the hazard of the adverse event on treatment status. The analysis incorporated the IPT weights and used a robust variance estimator. In order to estimate the cause-specific hazard, which is of etiological interest, subjects were censored on the occurrence of death. Treatment effects were estimated separately for patients aged 18–65 years and 66 years and older, as well as within each age group for the subset of patients with pre-existing diabetes.

All analyses were carried out independently at each study site, with each site remaining blinded to results from other sites until the findings were pooled. Meta-analyses were performed independently by a team member not involved in the site-level analyses (RP) using fixed-effect models with inverse variance weighting. The magnitude of between-site heterogeneity was estimated using the I^2 statistic (Higgins and Thompson, 2002). In a sensitivity analysis, the results were pooled using random-effects models.

2.7. Secondary analysis

To address concerns regarding treatment discontinuation and switches that would not be incorporated in our intention-to-treat analysis, we also performed a secondary analysis using a nested case–control analysis of our cohort. Cases were defined as subjects at risk of a hyperglycemic event, and were matched 5:1 on age, sex, calendar year, pre-existing diabetes, and schizophrenia, to controls who did not experience a hyperglycemic event. The event date served as the index date for the cases, and controls were assigned index dates of their matched cases. Antipsychotic exposure was defined based on the most recent prescription dispensed prior to the index date. A conditional logistic regression model was used to estimate the odds ratio for the adverse event, comparing the comparator agent to risperidone, after adjusting for the Romano index.

3. Results

3.1. Characteristics of subjects and exposures

The study involved 725,489 patients, 55% aged 66 years or older (Table 1). Five jurisdictions contributed to analyses of patients aged 18–65 years, most (75%) of whom resided in Quebec and British Columbia. Four of these sites had a sufficient number of patients to participate in the subgroup analyses involving patients with pre-existing diabetes. All eight sites contributed to analyses of older patients, two-thirds of whom resided in Quebec and Ontario, Canada's most populous provinces. Six of these sites participated in the subgroup analyses of diabetic patients. Forty-eight percent of the younger cohort was male and 5% had diabetes, compared with 39% and 19%, respectively, among the older patients.

Table 2 gives the distribution of study patients by initial drug therapy and age group. Twenty-four percent of younger patients received the reference drug, risperidone, compared with 39% of older patients. (Of note, in Canada, only risperidone has an approved indication for management of behavioural symptoms of dementia (BPSD) (Janssen Inc., 2013).) In contrast, 38% of younger patients and 19% of older patients received other atypical agents, which was quetiapine in 98.7% of those 18–65 years and 99.6% of those 66 years and older. Olanzapine was used in 15% and 13% of younger and older patients respectively.

3.2. Acute hyperglycemic emergency rates

There were 892 events reported overall among new users of antipsychotics: 283 events in patients aged 18–65 years; and 609 events in patients aged 66 years and older. In general, hyperglycemic emergencies were rare, ranging from approximately 1 per 1000 person years in patients aged 18–65 years to about 2 per 1000 person years in patients aged 66 years and older (Table 1). In those with pre-existing diabetes compared to those without, the rate of hyperglycemic emergencies was 8-fold higher (6.6 versus 0.85 per 1000 person years) among older patients, and 30-fold (11.5 versus 0.39 per 1000 person years) among patients age 18–65 years. In patients aged 18–65 years, 59.4% of events were admissions for DKA, 9.6% were for HHS, and 30.9% were for hyperglycemia. In contrast, these events were observed at similar frequencies among those aged 66 years and older (i.e., 29.4%, 33.7%, and 37.4%, respectively).

Overall, there was relatively little variation in crude event rates among the individual drug exposure groups (Table 2). Variation

Table 1
Number of patients and crude hyperglycemic emergency event rates according to age group, sex, diabetes status, and study site.

Characteristic	Number of patients (% column total)		Number of events (and crude event rate per 1000 person years, 95% CI)	
	Age 18–65 years	Age 66+ years	Age 18–65 years	Age 66+ years
Sex				
Male	154,095 (47.5)	158,132 (39.4)	132 (0.92, 0.76–1.07)	273 (2.30, 2.03–2.57)
Female	170,417 (52.5)	242,845 (60.6)	151 (0.95, 0.80–1.10)	336 (1.70, 1.52–1.88)
Diabetes				
Yes	16,793 (5.2)	75,970 (18.9)	172 (11.49, 9.78–13.21)	389 (6.64, 5.98–7.30)
No	307,719 (94.8)	325,007 (81.1)	111 (0.39, 0.31–0.46)	220 (0.85, 0.74–0.97)
Study site				
Nova Scotia	–	12,702 (3.2)	–	13 (1.38, 0.63–2.14)
Quebec	108,923 (33.6)	102,419 (25.5)	95 (0.94, 0.79–1.18)	157 (2.03, 1.71–2.35)
Ontario	–	154,695 (38.6)	–	301 (2.34, 2.07–2.60)
Manitoba	27,066 (8.3)	12,109 (3.0)	31 (1.21, 0.78–1.63)	9 (0.98, 0.34–1.62)
Saskatchewan	20,179 (6.2)	20,524 (5.1)	25 (1.29, 0.78–1.79)	35 (2.10, 1.41–2.80)
Alberta	–	26,557 (6.6)	–	25 (1.30, 0.79–1.81)
British Columbia	141,835 (43.7)	50,470 (12.6)	110 (0.80, 0.65–0.95)	51 (1.19, 0.86–1.52)
GPRD	26,509 (8.2)	21,501 (5.4)	22 (0.95, 0.55–1.34)	18 (1.38, 0.74–2.02)
Overall	324,512	400,977	283 (0.93, 0.82–1.04)	609 (1.92, 1.77–2.08)

CI: confidence interval.
GPRD: General Practice Research Database.

Table 2
Number of patients and crude hyperglycemic emergency event rates according to age group and drug exposure.

Drug exposure	Number of patients (% column total)		Crude event rate[a] (per 1000 person years, 95% CI)	
	Age 18–65 years	Age 66+ years	Age 18–65 years	Age 66+ years
Risperidone	76,212 (23.5)	158,019 (39.4)	0.78, 0.58–0.99	2.01, 1.77–2.26
Olanzapine	47,699 (14.7)	52,351 (13.1)	0.85, 0.58–1.13	1.87, 1.46–2.27
Other Atypical	123,971 (38.2)	75,514 (18.8)	0.93, 0.75–1.10	1.61, 1.30–1.93
Typical	76,630 (23.6)	115,091 (28.7)	1.03, 0.80–1.27	2.06, 1.75–2.37
Overall	324,512	400,977	0.93, 0.82–1.04	1.92, 1.77–2.08

CI: confidence interval.
[a] Rates are estimated based on event counts by exposure status, whereby suppressed small cells were assigned a value of 3.

was more striking among younger patients after stratifying by diabetes status (Table 3), where the drug-specific rates ranged from 5 to 14 per 1000 person years in those with diabetes versus 0.3 to 1 per 1000 person years in those without diabetes.

3.3. Comparative analyses

Based on fixed-effect meta-analyses, relative to new users of risperidone, there was no significant increase in risk of hyperglycemic emergencies among new users of our primary comparator, olanzapine, regardless of age or diabetes status (Table 4). Results were similar for typical antipsychotics in both age groups. However, other atypical agents (99% quetiapine) were associated with a significantly lower risk than risperidone in patients over age 66 years (adjusted hazard ratio [HR], 95% confidence interval [CI]: 0.69, 0.53–0.90). In older patients with pre-existing diabetes, both typical antipsychotics and other atypical antipsychotics were associated with a lower risk than risperidone (adjusted HR, 95% CI: 0.62, 0.41–0.95; and 0.68, 0.49–0.95; respectively). Site level results are presented in Web Figs. 1–12. Whereas findings were homogeneous across sites for the majority of our meta-analyses, significant heterogeneity existed for the analysis of olanzapine versus risperidone in older patients, both overall and in those with pre-existing diabetes ($I^2 = 49\%$, $p = 0.07$ and $I^2 = 64.4\%$, $p = 0.02$ respectively; Web Figs. 7 and 8). Meta-analyses using random effects models gave similar results. There were no statistical differences in outcomes between current use of olanzapine, other atypical, or typical agents compared to current use of risperidone on meta-analyses of our secondary nested case–control analyses. However, power was limited as some sites could not contribute as models did not converge due to small numbers (data not shown).

4. Discussion

In this study of over 725,000 patients newly exposed to antipsychotic medication, hyperglycemic emergencies were uncommon (in the range of 1–2 events per 1000 person years of exposure), but were relatively more frequent among those with pre-existing diabetes, in whom event rates approached 12 per 1000 person years. Despite prior evidence of potential higher risks of diabetes and hyperglycemia with olanzapine (Ramaswamy et al., 2006; Ramaswamy et al., 2007), in our large population-based sample we failed to find a significant increase in hyperglycemic emergencies among new olanzapine versus risperidone users, regardless of age or diabetes status. In contrast, older persons treated with other atypical antipsychotics (mainly quetiapine) experienced about 30% fewer events than those exposed to risperidone. Our findings highlight the importance of glucose monitoring in seniors initiating antipsychotic therapy, and suggest the need for further research to confirm the relative safety advantage with quetiapine.

While a link between antipsychotic treatment and hyperglycemia is well documented, prior studies have focused mainly on younger patients with schizophrenia, who may have a higher baseline risk of diabetes (Dixon et al., 2000). This association has made it difficult to separate the effects of the medication from those of the disease itself. Further, previous studies of seniors have been too small to demonstrate differences among individual medications, or to consider acute effects in the period immediately following treatment initiation. Indeed, evidence suggests that the majority of hyperglycemic emergencies occur in the first six months of antipsychotic therapy (Jin et al., 2002; Lipscombe et al., 2009). By restricting our analyses to new users, our study more accurately reflects the experience of patients and risks most likely attributable to antipsychotic therapy. By not doing so, one runs the risk of underestimating harms by including longer-term users who are less susceptible to adverse outcomes (Moride and Abenhaim, 1994).

Generally, prior studies among patients with schizophrenia have suggested greater metabolic risks with olanzapine (Ramaswamy et al., 2006, 2007) or atypical agents collectively (Smith et al., 2008) compared with typical antipsychotics. However, bias due to greater baseline risk of diabetes cannot be excluded in these studies, and evidence is unclear in older patients treated primarily for BPSD (Lipscombe et al., 2009, 2011). Our large study across multiple databases failed to demonstrate a significant increase in risk for hyperglycemic emergencies with olanzapine in younger or older patients. However, we did note substantial heterogeneity across sites for the comparison of olanzapine and risperidone in older patients. While some sites found a higher risk of hyperglycemic emergencies with olanzapine, the two largest sites contributing the greatest weight to the meta-analysis (Quebec and Ontario) reported hazard ratios close to unity (Web Figs. 7 and 8). The reasons for these differences are unclear. However, differences in provincial reimbursement policies may have been a contributing factor. Whereas no restrictions exist in Ontario and Quebec, the provincial drug benefit

Table 3
Crude hyperglycemic emergency event rates according to age group, diabetes status, and drug exposure.

Drug exposure	Crude event rate[a] (per 1000 person years, 95% CI)			
	Age 18–65 years		Age 66+ years	
	Diabetes (n = 16,793)	No diabetes (n = 307,724)	Diabetes (n = 75,970)	No diabetes (n = 325,007)
Risperidone	9.45, 6.32–12.59	0.36, 0.22–0.50	7.07, 6.00–8.14	0.85, 0.67–1.02
Olanzapine	9.62, 4.90–14.33	0.51, 0.30–0.73	6.74, 4.90–8.57	0.78, 0.49–1.08
Other Atypical	11.71, 9.01–14.41	0.30, 0.20–0.41	4.98, 3.76–6.20	0.67, 0.45–0.90
Typical	14.20, 10.23–18.18	0.46, 0.30–0.63	7.35, 5.95–8.76	1.03, 0.79–1.27
Overall	11.49, 9.78–13.21	0.39, 0.31–0.46	6.64, 5.98–7.30	0.85, 0.74–0.97

CI: confidence interval.
[a] Rates are estimated based on event counts by exposure status, whereby suppressed small cells were assigned a value of 3.

Table 4
Summary of the results of the fixed-effect meta-analyses.[a]

Drug exposure	Age 18–65 years				Age 66+ years			
	Overall		Diabetes		Overall		Diabetes	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Risperidone	1.00	–	1.00	–	1.00	–	1.00	–
Olanzapine	1.15	0.71–1.86	1.19	0.52–2.72	1.13	0.87–1.48	1.12	0.80–1.56
Other Atypical	0.94	0.64–1.38	0.89	0.45–1.68	0.69	0.53–0.90	0.68	0.49–0.95
Typical	0.95	0.61–1.54	1.09	0.61–1.95	1.03	0.73–1.45	0.62	0.41–0.95

HR: hazard ratio.
CI: confidence interval.
[a] Adjusted for: age; sex; calendar year of cohort entry; history of diabetes, schizophrenia and dementia; neighbourhood income quintile; Romano Comorbidity Index; number of hospitalizations, outpatient family physician consultations and outpatient psychiatric consultations in the year preceding cohort entry; and concurrent exposure to selected drugs that are markers of disease or could influence glucose control.

programmes in Saskatchewan and British Columbia (two of the provinces that reported increased risks) pay for olanzapine only when prescribed as second-line therapy. One might speculate that such patients are more vulnerable to decompensated glucose control due to untreated behavioural symptoms, thereby introducing a selection bias within these provinces. By examining this question across several health care settings simultaneously, our study was able to expose this potential bias and avoid misinterpretation that may have occurred in a single-centre study. These findings argue against a true relative increased risk of hyperglycemic emergencies with olanzapine, and highlight the possibility that selection bias may have contributed to an apparent increased risk in prior studies. The interpretation of these findings is limited by the heterogeneity of reimbursement policies across provinces, and further studies are needed.

In our study, the lowest risk of hyperglycemic emergencies was found in those patients treated with quetiapine (or rarely other newer atypical antipsychotics). While case reports have documented hyperglycemic events following quetiapine treatment (Koller et al., 2004; Takahashi et al., 2005; Marlowe et al., 2007), further research is needed to confirm whether quetiapine is in fact metabolically safer than other atypical agents. Meanwhile, quetiapine may be favoured over other agents when other clinical indications are similar in patients with increased risk for hyperglycemia.

Despite adjustment for multiple known and suspected confounders, we acknowledge that there is potential for residual confounding in our findings. For example, relative to patients with diabetes who received risperidone, those prescribed quetiapine may have had fewer unmeasured underlying risk factors for hyperglycemia or better adherence to their diabetes medications. We attempted to address these concerns by confining our analyses to new users of antipsychotics among patients who were likely to be receiving the medications for similar indications. Second, we limited our outcome to hospital visits for hyperglycemic emergencies, which are likely to be largely non-discretionary and for which coding quality should be good (Bobo et al., 2011). Third, to help control for effects of important factors such as dementia, schizophrenia, and diabetes severity, we adjusted for treatment characteristics at baseline. Nevertheless, as risperidone is the only antipsychotic with an approved indication for BPSD (Janssen Inc., 2013), selection biases could favour some agents. However, that we observed relatively better outcomes among both users of other atypical agents and older typical agents argues against important biases. Given that we were only able to capture drug use in the year before study entry, we could not determine whether some patients had more remote previous exposure to antipsychotic agents. Our findings also do not apply to patients taking multiple antipsychotic agents. Finally, despite the large size of our study, power remains a limitation, as the 95% confidence intervals for many analyses include clinically important benefits and harms.

In sum, our large, multicentre study found hyperglycemic emergencies to be rare after initiating antipsychotic therapy, although patients with diabetes were at relatively greater risk. Compared to older patients treated with risperidone, hyperglycemic emergencies may be less frequent with quetiapine. While our findings require replication, they highlight the importance of glucose monitoring in seniors initiating antipsychotic therapy, particularly in those with pre-existing diabetes.

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Contributors

All authors contributed to and have approved the final manuscript.

L. Lipscombe — conceptualized and designed the study, conducted the literature review, wrote the manuscript.

P. Austin — contributed to the study design, developed the analytic plan, edited and approved the manuscript.

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D. F. Blackburn — contributed to the study design, directed data collection and analysis at Saskatchewan site, edited and approved the manuscript.

L. Blais — contributed to the study design, directed data collection and analysis at Quebec site, edited and approved the manuscript.

L. Bresee — contributed to the study design, directed data collection and analysis at Alberta site, edited and approved the manuscript.

K.B. Filion — contributed to the study design, directed data collection and analysis for CPRD database, edited and approved the manuscript.

Y. Kawasumi — contributed to the study design, directed data collection and analysis at British Columbia site, edited and approved the manuscript.

P. Kurdyak — contributed to the conceptualization of the study, literature review, and study design, edited and approved the manuscript.

R.W. Platt — contributed to the study design and analytic plan; performed the meta-analyses, edited and approved the manuscript.

H. Tamim — contributed to the study design, directed data collection and analysis at Nova Scotia site, edited and approved the manuscript.

J.M. Paterson — contributed to the study design, directed data collection and analysis at Ontario site, prepared tables and co-wrote manuscript.

The CNODES Investigators — supported the overall design and execution of the study, provided support for the study, and approved the manuscript.

Conflict of interest

Ethics approval was obtained from the research ethics board of the university or hospital to which each participating research team is affiliated. The following authors report no competing interests: Lorraine Lipscombe, Michael Paterson, Peter Austin, Lauren Bresee, Kristian Filion, Yuko Kawasumi, Hala Tamim, and Robert Platt. Silvia Alessi-Severini reports receiving an unrelated unrestricted research grant from Pfizer. David Blackburn reports his position was created through the unrestricted financial support of AstraZeneca Canada, Merck Frosst Canada, Pfizer Canada, and the Province of Saskatchewan's Ministry of Health. Lucie Blais reports receiving unrelated research grants from AstraZeneca, Pfizer, Sanofi-Aventis, Novartis and Merck Frosst. She also holds an AstraZeneca Research Chair in Respiratory Health.

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Appendix 1. Category, name, WHO ATC code, and route of study antipsychotic agents

Name	WHO ATC code	Route
Atypical		
Risperidone (reference)	N05AX08	Oral or IM (long-acting)
Olanzapine	N05AH03	Oral or IM (short-acting)
Clozapine	N05AH02	Oral
Quetiapine	N05AH04	Oral
Ziprasidone	N05AE04	Oral
Paliperidone	N05AX13	Oral
Aripiprazole	N05AX12	Oral
Typical		
Chlormezanone	M03BB02	Oral
Chlorpromazine	N05AA01	Oral or IM
Chlorprothixene	N05AF03	Oral
Flupenthixol	N05AF01	Oral or IM (long-acting)
Fluphenazine	N05AB02	Oral or IM (long-acting)
Fluspirilene	N05AG01	IM (short-acting)
Haloperidol	N05AD01	Oral or IM (short- and long-acting)
Levomepromazine/ Methotrimeprazine	N05AA02	Oral or IM (short-acting)
Loxapine	N05AH01	Oral or IM (short-acting)
Mesoridazine	N05AC03	Oral
Perphenazine	N05AB03	Oral or IM (short-acting)
Pimozide	N05AG02	Oral
Pipotiazine	N05AC04	Oral or IM (short-acting)
Tetrabenazine	N07XX06	Oral
Thiopropazate	N05AB05	Oral
Thioproperazine	N05AB08	Oral or IM (short-acting)
Thioridazine	N05AC02	Oral
Thiothixene	N05AF04	Oral
Trifluoperazine	N05AB06	Oral
Zuclopenthixol	N05AF05	Oral or IM (long-acting)

ATC: Anatomical Therapeutic Chemical classification; IM: intramuscular; WHO: World Health Organization.

Appendix 2. Diagnosis codes for hyperglycemic emergencies

Endpoint	ICD-9	ICD-10
Hyperglycemia	790.29	R739
Diabetes ketoacidosis (DKA)	250.10, 250.11, 250.12, 250.13	E10.1, E11.1, E13.1, E14.1
Hyperosmolar hyperglycemic state (HHS)	250.20, 250.21, 250.22, 250.23	E11.0, E13.0, E14.0

Appendix 3. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.01.043.

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